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10/621,326	07/18/2003	Arnold Hoffman	HOFFMAN9	2518

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/621,326	HOFFMAN ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1-4,6-9,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,10-13 and 16* is/are rejected.

7)☒ Claim(s) 11 & 13 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-16 are currently pending and are the subject of this Office Action. Claims 1-4, 6-9 and 14-15 are withdrawn from consideration as being drawn to non-elected subject matter. This is the first Office Action on the merits of the application.

Election/Restrictions

Applicant's election with traverse of Group II, claims 5-16 in the reply filed on 3/16/2006 is acknowledged. The traversal is on the ground(s) that the claims of Group I are simply broader and would encompass the claims of Group II. This is not found persuasive because the claims of Group II require at least two agents whereas the claims of group I only require one agent. As discussed in the restriction requirement mailed on 2/17/2006, the method in Group I does not require the synergistic combination of the method of Group II. Thus, while the methods of Groups I and II achieve the same objective, *i.e.* treatment of a tumor by decreasing the $[GSH]^2/[GSSG]$ ratio in malignant cells of the tumor, they do so by employing different method steps. Moreover, the search required for the method of Group II would not be required for the method of Group 1. For these reasons, the inventions of Groups I and II are considered to be independent and distinct, and the requirement is still deemed proper and is therefore made FINAL. Claims 1-4 are withdrawn from consideration as being drawn to non-elected subject matter.

Further, the species election requirement is still deemed proper. Applicant's election with traverse of "Species 6" consisting of a synergistic combination of three agents (i, iii, and iv)

as recited in claim 5 is acknowledged. Specifically, applicants have elected, with traverse, the synergistic combination of disulfiram (i), buthionine sulfoximine (iii) and carmustine (iv). Applicants traverse on the grounds that examination of at least "some species other than the elected species would not constitute a 'serious burden'". This argument is not persuasive because the compounds recited in the generic claims have different structures and different mechanisms of action (*e.g.* some inhibit the GCS enzyme whereas other inhibit the GR enzyme). As such, to search the entire scope of the claims would present an undue search burden on the examiner for the reasons set forth in the original election of species requirement. The requirement is still deemed proper and is therefore made FINAL. Claims 6-9 and 14-15 are withdrawn from consideration as being drawn to non-elected species. Claims 5, 10-13 and 16 read on the elected species and will be examined on the merits.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Israel on 1/18/2002. It is noted, however, that applicant has not filed a certified copy of the 140970 application as required by 35 U.S.C. 119(b).

Claim Objections

Claims 11 and 13 are objected to because of the following informalities: in line 1 of each respective claim, the word "at" appears to be missing between the words "said" and "least". Appropriate correction is required.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 10-13 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of treating a tumor comprising administering a synergistic combination of "at least two agents", wherein the agents are selected from the classes consisting of: (i) an agent that oxidizes GSH; (ii) an agent that form an adduct or conjugate with GSH; (iii) an agent that inhibits the GCS enzyme; and (iv) an agent that inhibits the glutathione reductase enzyme.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of the complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present is biological activity. There is no description of structural characteristics that are required to retain biological activity. Accordingly, in the absence of sufficient recitation of distinguishing

characteristics, the specification does not provide adequate written description of the claimed genus (agents of groups i-iv recited in claim 5).

Vas-Cath, Inc. v. Mahurkar, 19USPQ2d 111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed *supra*, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of agents (i), (ii), (iii) or (iv), and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or synthesis. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or synthesizing it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only the specific compounds disclosed in the specification (*i.e.* those agents identified by name on pages 14-16, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes it clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see *Vas-Cath* at page 1115). See also *In re Barker*, 559 F.2d 588, 591, 194 USPQ 470, 472 (CCPA 1977) (a specification may be sufficient to enable one skilled in the art to make and use the invention, but still fail to comply with the written description requirement).

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 10-13 and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the limitation "$[GSH]^2/[GSSG]$" in line 3. The first recitation of an abbreviation in the claims must include the full meaning of the abbreviated term. Claims dependent from claim 5 are included in this rejection.

Claim 5 recites the administration of "an effective amount" of a synergistic combination of at least two agents. This limitation is indefinite because it is not clear what the amount being administered is effective for. The preamble of the claim is not linked to the body of the claim in such a way as to clearly convey that the "effective amount" being administered is effective to treat the condition recited in the preamble. The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. *In re Fredericksen* 213 F.2d 547, 102 USPQ 35 (CCPA 1954). Claims dependent from claim 5 are included in this rejection.

Claim 5 recites that administration of a synergistic combination of at least two agents that decrease the $[GSH]^2/[GSSG]$ ratio "in the malignant cells of said tumor". However, the preamble of the claim does not limit the treatment to malignant tumors. Thus, claim 5 is

indefinite because it is not clear whether the tumor being treated is benign or malignant. Claims dependent from claim 5 are included in this rejection.

Claim 16 recites the limitation wherein the synergistic combination of claim 5 is administered continuously for a period of time within the range of "from about 15 to about 75 hours." The claim is indefinite because "from" and "about" are mutually exclusive and have opposite meanings. "From" implies a definite lower limit, in this case 15 hours. However, "about" implies that the lower limit can be some other value around 15 hours. When used together, "from about" renders the claim indefinite because the metes and bounds of the lower limit are not clear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 5, 10-13 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,589,987 (Issued July 8, 2003; Filed Sept. 8, 1999) in view of Huang *et al.* (The FASEB Journal, 2001, vol. 15, pages 19-21; published online 11/9/2000), Ali-Osman *et al.* (Mol. Pharm., 1996, vol. 49, pages 1012-1020) and Nagendra *et al.* (Alcohol, 1994, vol. 11, pages 7-10).

The instant claims are drawn to the treatment of tumors comprising administering disulfiram (oxidizes GSH), buthionine sufloximine (BSO; inhibits GCS enzyme) and carmustine (BCNU; inhibits GR enzyme). Applicants claim that administration of "at least two agents that decrease the $[GSH]^2/[GSSG]$ ratio" in the malignant cells of the tumor will lead to treatment of said tumor in a subject (see instant claim 5).

'987 discloses that disulfiram inhibits the growth of cancer cells (Abstract; col. 2, lines 38-44). Disulfiram can also be administered in combination with another anticancer agent (col. 3, lines 10-13 and col. 7, lines 8-18).

Huang *et al.* disclose that the glutathione (GSH) level in hepatocytes increases during active proliferation (Abstract). The authors evaluated whether a similar increase is found in hepatocellular carcinoma (HCC). It is disclosed that GSH levels doubled in HCC as compared to normal liver (page 19). HepG2 liver cancer cells were grown with varying concentrations of cysteine and it was found that cell growth increased with increasing cysteine concentration (page 19, right column). Further, BSO treatment decreased GSH levels and rates of growth. Cells treated with BSO for 24 hours had significantly lower DNA synthesis than controls (page 19, right column). The authors disclose that GSH has been found to be elevated in a number of drug-resistant tumor cell lines including prostate, ovarian, lung and colorectal cancers (page 20,

right column). Increased γ-L-glutamyl-L-cysteine synthetase (GCS) activity was found in the majority of these resistant tumor cells. The authors conclude that "an increase in the cellular GSH content may change the thiol-redox status of the cell that is proportional to $[GSH]^2/[GSSG]$" (page 21, right column). This change in redox state may then "affect the expression or activity of factors important for cell cycle progression".

Ali-Osman *et al.* disclose that depletion of GSH by BSO (currently being explored as a means of enhancing the efficacy of cancer chemotherapy) in human malignant glioma cells potentiated the cytotoxicity of BCNU (Abstract). Figure 1 demonstrates that GCS is significantly inhibited by BSO (page 1015). Further, exposure to BSO significantly depleted GSH (Figure 2, page 1015). Although BSO had no effect on cell survival, it did sensitize the cell lines to treatment with BCNU (Table 1, page 1017 and Figure 6, page 1018). GSH depletion is a major mechanism by which BSO enhances cellular alkylator sensitivity although there is evidence that BSO may increase drug sensitivity by other mechanisms (page 1018, right column).

Nagendra *et al.* disclose that chronic administration of disulfiram to rats affects GSH metabolism (Abstract). Administration of disulfiram led to a decrease in GSH with a concomitant increase in GSSG content. Brain glutathione reductase activity was also significantly depleted. The authors conclude that treatment with disulfiram decreases GSH content with a concomitant increase in GSSG level and perturbs the GSH/GSSG redox status, inducing oxidative stress on the brain.

In view of the above disclosures, the instant claims would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. It is well known in the art

that administration of BSO depletes GSH content and enhances the cytotoxicity of BCNU. Further, disulfiram has been shown to inhibit cancer cell proliferation and decrease GSH with a concomitant increase in GSSG (thereby decreasing the $[GSH]^2/[GSSG]$ ratio as recited in instant claim 5). It would have been obvious to combine disulfiram, BSO and carmustine to treat tumors because from the disclosures of the '987 patent, Huang *et al.*, Ali-Osman *et al.* and Nagendra *et al.* it is clear that disulfiram is effective at inhibiting cancer cell proliferation and decreasing GSH cell content has a significant effect on the cytotoxicity of the chemotherapeutic drug carmustine. Thus, the skilled artisan would be imbued with at least a reasonable expectation that administering disulfiram would be an effective treatment for tumors while administration of BSO would decrease GSH content resulting in the sensitization of tumors to BCNU treatment.

Although ample motivation to combine the references is found in the teachings of the individual references as discussed *supra*, difulfiram and carmustine (*i.e.* BCNU) are individually known in the art as agents for treating cancers, whose efficacy when administered alone is well established for the treatment of a large number of neoplasias and metastasis. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as

discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption. Further, the addition of BSO to a composition of disulfiram and carmustine would have been obvious given the teachings of Ali-Osman *et al.* who disclose that BSO enhances the anticancer activity of BCNU.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

August 22, 2006

Ardin H. Marschel 8/28/06
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SUPERVISORY PATENT EXAMINER